SMALLPOX VACCINATIONS IN THE MANAGEMENT OF RECURRENT HERPES SIMPLEX: A CONTROLLED EVALUATION*

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The management of herpes simplex usually offers no problem except in those instances in which the patient is afflicted with recurrent attacks. We have observed cases with lesions occurring as frequently as every two weeks, although often the intervals are greater. In any event, the temporary disfigurement produced can be a source of considerable distress. It is this which leads the patient to seek aid, aid in the prevention of further attacks.

What can the physician offer? One form of treatment dates back to the work of Gildemeister and Herzberg (1) who, in 1925, produced a relative immunity of the rabbit cornea to smallpox vaccine by previous inoculation with the virus of herpes simplex. On the basis of these results they suggested that the herpes virus might be a variant of that of smallpox. The following year Heymann (2) cited the observations of Jenner on the inhibition of the smallpox vaccine pustule in patients with herpes. In 1928, Freund (3) reported favorable results with cowpox lymph in the management of seven patients with recurrent herpes simplex. However, Bedson and Bland (4), in the same year, on the basis of their studies on guinea pigs concluded that the virus of herpes simplex and of vaccinia are unrelated. Despite the experimental results of Bedson and Bland, clinical investigations by Minami and Ohmichi (5) and Wise and Sulzberger (6) supported the concept that smallpox vaccinations helped to prevent attacks of herpes simplex.

Foster and Abshier (7), in 1937, reported on 35 patients with regular and frequent attacks of herpes simplex. Vaccinations were given at two week intervals, most patients receiving a total of four. In only five patients (14 per cent) did recurrence follow this therapy. Ullman (8), in 1939, described beneficial effects in four cases from a single smallpox vaccination. Davis (9), in 1940, reported good results in his series of 14 cases treated with multiple vaccinations.

In 1941, Woodburne (10) described his results in 22 cases of herpetic stomatitis treated with two to fifteen vaccinations. Recurrence occurred in eight and in each instance cure was induced by one to seven additional vaccinations. Keddie and coworkers (11), on the other hand, observed no decrease in the incidence of herpes simplex in a series of patients given a single vaccination a few days to a few weeks prior to artificial fever therapy. In discussion of this paper, Kile (12) stated that smallpox vaccinations were of no value in the management of recurrent herpes simplex while Schoch (13) and Seale (14) each stated that they had obtained satisfactory results with this therapeutic approach.

Arnold (15), in 1944, reported on 14 cases of recurrent herpetic stomatitis with favorable response to intradermal injections of smallpox vaccine. Anderson (16), in 1945, focused attention on a probable etiologic relationship between herpes simplex and erythema multiforme. During the preceding 10 years he had found multiple vaccinations of value in about 80 per cent of his cases of recurrent herpes simplex. Accordingly, he used this same procedure for the prevention of erythema multiforme associated with herpes simplex and also in prevention of recurrent erythema multiforme not associated with herpes. He found this therapy definitely of value, particularly in those cases which were preceded by herpes simplex.

Pepys (17), in 1946, reported on two patients with recurrent herpes simplex, one with attacks every two months for 45 years and the other with attacks every two to three months over a period of 20 years; no further outbreaks occurred after three vaccinations.

In 1947 we began treating all our cases of recurrent herpes simplex with smallpox vaccinations. In 1954 we reported our results in a total of 68 patients (18). This was by no means a very large series, but, nevertheless, it was the largest thus far reported. Smallpox vaccinations were administered by the multiple puncture technic at

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two week intervals. The number varied from two to eight, most patients receiving two or three. The duration of disease prior to therapy varied from one month to 20 years, most patients having had recurrent attacks for four to five months before the start of treatment. The number of attacks before treatment varied from two to approximately fifty. Frequency of attacks prior to therapy varied from every 2 to every 32 weeks, 41 patients having had their attacks at two to three months intervals. Of the 68 patients in the series, in only 9 did recurrence occur following the course of treatment and in seven others there was some question as to possible recurrence. In summary, 52 patients (76.5 per cent) definitely had no subsequent attacks during a lengthy follow-up period.

In attempting to explain these results we considered three possibilities. The first was that the living virus in cowpox lymph stimulated the formation of antibody to herpes simplex virus, this increased titer preventing recurrence. The validity of this concept has, however, been questioned by Burnet (19) who maintained that the high level of neutralizing antibody reached within a few weeks after primary infection remains fairly constant for life. Furthermore, with an already high titer stimulation of antibody formation would appear to be of little value. However, Jawetz, Allende and Coleman (20) have demonstrated that a given individual may show considerable fluctuation of antibody level. Wenner (21) observed complete disappearance of antibody from the blood of a child seven months after an attack of Kaposi's varicelliform eruption. Buddingh and co-workers (22) studied the neutralizing antibody level in 12 children with primary herpetic gingivostomatitis. Antibodies were first detected from the fourth to seventh day following onset of illness, with a rapid increase thereafter. In the majority of cases the maximum level was reached three to four weeks after onset. However, this maximum was not maintained indefinitely, the titer subsequently dropping to lower levels. In one of their cases they noted a significant increase in neutralizing antibody on two occasions; in each instance the increase occurred during an episode when virus was recovered from the patient although no evidence of infection was discernible. Geller, Coleman and Jawetz (23) injected viable herpes simplex virus intravenously into 9 subjects. In 4 of these, this was followed by a significant rise in antibody level.

These reports suggest that at least in some individuals there is fluctuation in amount of antibody and that Burnet's concept of a high fixed level of antibody may be questioned. Can one postulate, therefore, that it is a fall in antibody titer that allows reactivation of virus in recurrent attacks of herpes simplex? Such a hypothesis is appealing. However, Scott and co-workers (24) did neutralizing antibody determinations in three adults with recurrent herpes simplex and found that regardless of attacks the level of antibodies remained approximately constant in a given individual. Blank and Rake (25) have expressed doubt that attempts to increase the titer of serologic antibodies will be of value in preventing recurrences. They refer to patients with frequent attacks whose sera when diluted 500 times would still rapidly inactivate herpes virus; nevertheless, a million or more virulent virus particles per milliliter of fluid could be observed within their lesions.

On the basis of the experimental evidence now available, the role of neutralizing antibody in recurrent herpes simplex is not clearly established. In any event, it appears unlikely that any benefit obtained from the use of vaccination can be attributed to stimulation of antibody formation.

The second possible explanation we considered at the time of our original report was that vaccinations might be beneficial as the result of "suggestion". Such a concept had been proposed by Ullman (8) and by Blank and Brady (26). We were however inclined at the time to discount the role of "suggestion" and to favor the opinion expressed by Wise and Sulzberger (27) to the effect that vaccination might act by changing tissue response in some unknown way.

INVESTIGATIVE STUDY

During the past three years we have attempted, by means of a controlled series, to evaluate the possible role of "suggestion". We divided our patients with recurrent herpes simplex into two groups. One was given a course of vaccinations with active smallpox vaccine. The second received heat-inactivated vaccine.* The former was labeled X-0456, the latter X-0457. The person

* Both active and inactive vaccine were supplied through the courtesy of Parke, Davis & Company, Detroit, Michigan.

administering the medication was not aware of which of the two was the active and which the inactive vaccine. A total of 57 patients are included in the series, 34 treated with active vaccine and 23 with inactive vaccine.

Vaccinations were administered by the multiple puncture technic and were usually given every two weeks. The total number received by each subject in the active group ranged from four to twelve, with an average of 7.5. The number given to the inactive group, with one exception, ranged from five to ten, with an average of 8. One of the inactive group received only one vaccination; this patient will be discussed in greater detail later. All patients were white, with 23 males and 14 females in the active group as compared to 11 males and 12 females in the inactive group. The age span in the active group was 8 to 60 years, the average being 27.8, while in the inactive group it was 7 to 60 years, with an average of 28 years. As can be seen from the table, the duration

	Duration of Disease Before Therapy (months)	Number of Attacks Before Therapy (months)	Frequency of Attacks Before Therapy (weeks)
Active	4 to 120 Average: 8	2 to 72 Average: 7	3 to 26 Average: 8
Inactive	2 to 108 Average: 14	2 to 48 Average: 6	3 to 52 Average: 10

of disease before therapy and the number and frequency of attacks were approximately the same for the two groups. Except for a greater proportion of males in the active group, the two series of patients were approximately the same.

RESULTS

Of the 34 patients in the active group no recurrence was observed in 23, or 67 per cent, over a follow-up period of 6 to 28, months, with an average follow-up of 20 months. Of the 23 patients in the inactive group no recurrence occurred in 12, or 52 per cent, over a follow-up period of 6 to 25 months, with an average of 20 months. It should be mentioned that in both groups there were patients who although showing recurrence reported that their subsequent attacks were less frequent and less severe than those prior to vaccination. One patient in the inactive group was a 29 year old female who had had monthly pre-menstrual attacks for four years. Following a single vaccination she was free of lesions for five months before her next outbreak of herpes.

DISCUSSION

We regret that the number of patients in our series is small and that the validity of our results may therefore be questioned. Nevertheless, the fact that 52 per cent of those treated with inactive vaccine were "cured" as compared to the only slightly better figure of 67 per cent obtained with active vaccine suggests that the psychotherapeutic factor may be the important one. It might be pointed out that these figures are different from those which we reported in July 1958 in our discussion (28) of the paper presented by G. Douglas Baldridge in the Dermatology Section of the meeting of the American Medical Association. At that time we concluded that although "suggestion" was a definite factor in some cases, in most instances vaccination probably achieved its beneficial effect by inducing some alteration within the body tissues so as to make them more resistant to the virus of herpes simplex. However, statistical analysis and a longer follow-up period has led to the change in our results.

There are two points that we would like to bring up at this time. The first concerns the occurrence of spontaneous cure. It certainly cannot be denied that in some of our cases spontaneous cure may have taken place. However, the long duration and high frequency of attacks prior to therapy would not make this too likely. It is, of course, to be assumed that spontaneous cure would occur as frequently in one group as in the other. Secondly, we would like to make clear the fact that the negligible difference in results observed in the two series does not indicate that "suggestion" is necessarily the responsible factor. It only proves that inoculation of vaccine containing living cowpox virus is not appreciably better than inoculation of vaccine containing heat-inactivated virus. We can only conclude, therefore, that smallpox vaccinations are beneficial due 1. to inoculation of a foreign protein or some other substance within the vaccine, 2. to "suggestion" or 3. both.

We must confess that when we started this investigation we were somewhat biased and expected that our results with the active vaccine would be superior to those obtained with the inactive one. Accordingly, we failed to include a second control, namely inoculation of normal saline. Had this been done our study would have

been more conclusive. We have recently started a new series of patients with recurrent herpes simplex on inoculations of normal saline in an attempt to throw further light on this somewhat beclouded subject.

SUMMARY

Patients with recurrent herpes simplex were divided into two groups. The first was treated with multiple smallpox vaccinations. The second was treated in similar fashion except that the vaccine used had been inactivated by heat. Fifty-two per cent of those given inactive vaccine remained free of attacks during the follow-up period. Sixty-seven per cent of those given the active vaccine remained free of attacks.

Since the difference in results is negligible one must conclude that benefit obtained from vaccination is probably due to inoculation of foreign protein or other substance within the vaccine, to "suggestion" or possibly to both. It is hoped that future studies will help us to arrive at a more specific conclusion.

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